

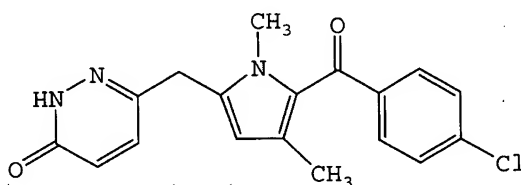
What is claimed is:

1. A method for the treatment, prevention, or inhibition of a CNS disorder, pain and inflammation, or an inflammation-associated disorder in a subject in need of such treatment, prevention, or inhibition, comprising administering a cyclooxygenase-2 selective inhibitor or prodrug thereof and a compound selected from the group consisting of duloxetine, venlafaxine and atomoxetine to the subject.
2. The method according to claim 1, wherein administering the cyclooxygenase-2 selective inhibitor or prodrug thereof and the duloxetine, the venlafaxine or the atomoxetine together comprises an effective method for the treatment, prevention, or inhibition of a CNS disorder, pain and inflammation, or an inflammation-associated disorder.
3. The method according to claim 1, wherein the venlafaxine is provided as a racemic mixture thereof.
4. The method according to claim 1, wherein the venlafaxine is an R isomer thereof.
5. The method according to claim 1, wherein the venlafaxine is an S isomer thereof.
6. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor or prodrug thereof has a cyclooxygenase-2  $IC_{50}$  of less than about 0.2  $\mu\text{mol/L}$ .
7. The method according to claim 6, wherein the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof has a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least about 2.
8. The method according to claim 7, wherein the cyclooxygenase-2 selective inhibitor or prodrug thereof has a cyclooxygenase-2  $IC_{50}$  of less than about 0.2  $\mu\text{mol/L}$  and also has a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least about 100.

9. The method according to claim 6, wherein the cyclooxygenase-2 selective inhibitor or prodrug thereof has a cyclooxygenase-1  $IC_{50}$  of at least about 1  $\mu\text{mol/L}$ .

10. The method according to claim 9, wherein the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof has a cyclooxygenase-1  $IC_{50}$  of at least about 10  $\mu\text{mol/L}$ .

11. The method according to claim 6, wherein the cyclooxygenase-2 selective inhibitor comprises 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, having the formula:

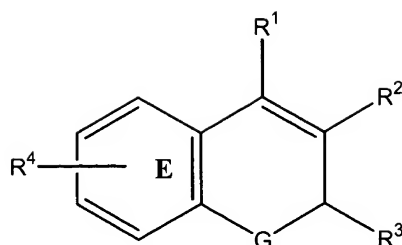


15 or a prodrug thereof.

12. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises a chromene.

13. The method according to claim 12, wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of substituted benzothiopyrans, dihydroquinolines, and dihydronaphthalenes having the general formula:

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wherein G is selected from the group consisting of O, S, and NR<sup>a</sup>;

wherein R<sup>a</sup> is alkyl;

wherein R<sup>1</sup> is selected from the group consisting of H and aryl;

5        wherein R<sup>2</sup> is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxy carbonyl;

          wherein R<sup>3</sup> is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

10       wherein R<sup>4</sup> is selected from the group consisting of one or more radicals selected from H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroaryl amino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

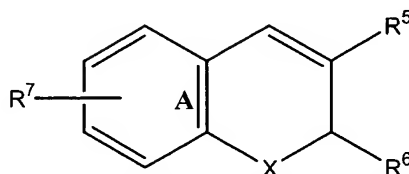
20       or wherein R<sup>4</sup> together with ring E forms a naphthyl radical;

          or an isomer thereof; and

          including the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

14. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises a compound having the formula:

wherein:



- 5 X is selected from the group consisting of O, S and  $\text{NR}^b$ ;  
 $\text{R}^b$  is alkyl;  
 $\text{R}^5$  is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;  
 $\text{R}^6$  is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein haloalkyl, alkyl, aralkyl, cycloalkyl, and aryl and each is independently optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and  
 $\text{R}^7$  is one or more radicals selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamine, heteroarylalkylamine, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein  $\text{R}^7$  together with ring A forms a naphthyl radical;  
 or an isomer or prodrug thereof.

15. The method according to claim 14, wherein:  
 25 X is selected from the group consisting of oxygen and sulfur;  
 $\text{R}^5$  is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

$R^6$  is selected from the group consisting of lower haloalkyl, lower cycloalkyl and phenyl; and

$R^7$  is one or more radicals selected from the group of consisting of hydrido, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, 6-membered-nitrogen containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl;

or wherein  $R^7$  together with ring A forms a naphthyl radical; or an isomer or prodrug thereof.

16. The method according to claim 14, wherein:

$R^5$  is carboxyl;

$R^6$  is lower haloalkyl; and

$R^7$  is one or more radicals selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or wherein  $R^7$  together with ring A forms a naphthyl radical;

or an isomer or prodrug thereof.

17. The method according to claim 14, wherein:

$R^6$  is selected from the group consisting of fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, and trifluoromethyl; and

$R^7$  is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropoxy, *tert*butyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-  
5 dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl,  
10 benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl and phenyl; or wherein  $R^2$  together with ring A forms a naphthyl radical;

or an isomer or prodrug thereof.

18. The method according to claim 14, wherein:

$R^6$  is selected from the group consisting trifluoromethyl and  
15 pentafluoroethyl; and

$R^7$  is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-  
20 dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, and phenyl; or wherein  $R^7$  together with ring A forms a naphthyl radical;

25 or an isomer or prodrug thereof.

19. The method according to claim 14, wherein the cyclooxygenase-2 selective inhibitor comprises:

- a) 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- b) 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic  
30 acid;

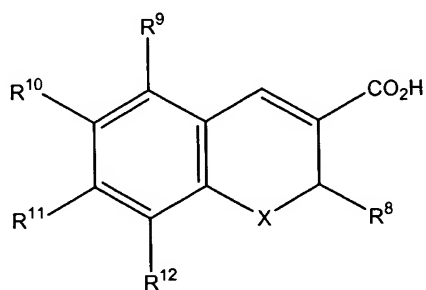
- c) 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- d) 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 5 e) 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- f) 2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid ;  
7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- g) 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 10 h) 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- i) 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- j) 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- k) 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 15 l) 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- m) 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n) 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 20 o) 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p) 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- q) 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 25 r) 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- s) 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- t) 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- u) 2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid;

- v) 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- w) 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 5 x) 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- y) 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- z) 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 10 aa) 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- bb) 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 15 cc) 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- dd) 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- ee) 6-[[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 20 ff) 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- gg) 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 25 hh) 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- ii) 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- jj) 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
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- kk) 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- ll) 8-chloro-6-[[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 5 mm) 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- nn) 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- oo) 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 10 pp) 6,8-dichloro-(S)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- qq) 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- rr) 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 15 ss) 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- tt) 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid; and
- 20 uu) 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid; or a prodrug of such compound.

20. The method according to claim 6, wherein the cyclooxygenase-2 specific inhibitor comprises a compound having the formula:



wherein:

X is selected from the group consisting of O and S;

R<sup>8</sup> is lower haloalkyl;

R<sup>9</sup> is selected from the group consisting of hydrido, and halo;

5        R<sup>10</sup> is selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, and 6-membered nitrogen-containing  
10       heterocyclosulfonyl;

R<sup>11</sup> is selected from the group consisting of hydrido, lower alkyl, halo, lower alkoxy, and aryl; and

R<sup>12</sup> is selected from the group consisting of the group consisting of hydrido, halo, lower alkyl, lower alkoxy, and aryl;

15       or an isomer or prodrug thereof.

21.    The method according to claim 20, wherein:

R<sup>8</sup> is selected from the group consisting of trifluoromethyl and pentafluoroethyl;

20       R<sup>9</sup> is selected from the group consisting of hydrido, chloro, and fluoro;

R<sup>10</sup> is selected from the group consisting of hydrido, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, and morpholinosulfonyl;

25       R<sup>11</sup> is selected from the group consisting of hydrido, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, and phenyl; and

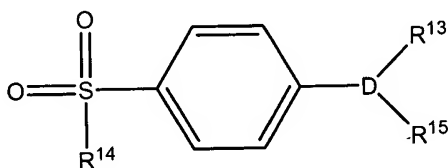
R<sup>12</sup> is selected from the group consisting of hydrido, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, and phenyl;

30       or an isomer or prodrug thereof.

22. A method of treating or preventing a cyclooxygenase-2 mediated disorder in a subject, said method comprising treating the subject having or susceptible to said disorder with a therapeutically-effective amount of a combination of duloxetine and a compound or salt of any of the compounds described in any one of claims 6 – 21, venlafaxine and a compound or salt of any of the compounds described in any one of claims 6 – 21 or a combination of atomoxetine and a compound or a salt of any of the compounds described in any one of claims 6 – 21.

23. The method according to claim 2, wherein the cyclooxygenase-2 mediated disorder is selected from the group consisting of a CNS disorder, inflammation, arthritis, pain and fever.

24. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises a material selected from the class of tricyclic cyclooxygenase-2 selective inhibitors represented by the general structure:



wherein:

D is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

R<sup>13</sup> is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R<sup>13</sup> is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl,

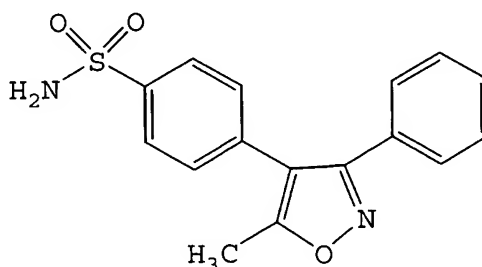
haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

R<sup>14</sup> is selected from the group consisting of methyl and amino; and

5 R<sup>15</sup> is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocycloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxy carbonyl, arylcarbonyl, aralkylcarbonyl, 10 aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxy carbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N- arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N- arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylmino, 15 aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N- alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylamino sulfonyl, arylsulfonyl, and N-alkyl-N- arylaminosulfonyl;

20 or a prodrug thereof.

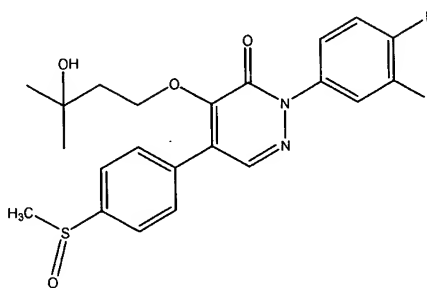
25. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises valdecoxib, having the following structure:



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or a prodrug thereof.

26. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises a compound having the structure:

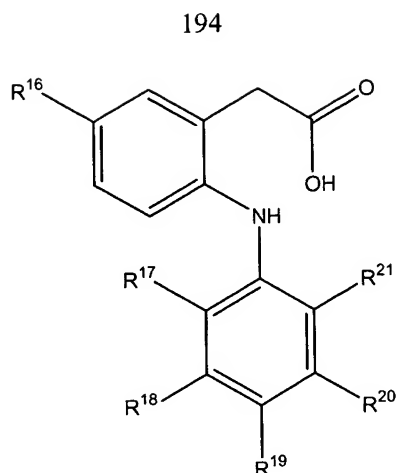


or a prodrug thereof.

27. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, JTE-522, deracoxib, a chromene, a chroman, parecoxib, valdecoxib, etoricoxib, rofecoxib, N-(2-cyclohexyloxynitrophenyl)methane sulfonamide, COX189, ABT963, meloxicam, BMS-347070, prodrugs of any of them, and mixtures thereof.

28. The method according to claim 27, wherein the cyclooxygenase-2 selective inhibitor comprises celecoxib or a prodrug thereof.

29. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises a phenylacetic acid derivative represented by the general structure:



wherein  $R^{16}$  is methyl or ethyl;

$R^{17}$  is chloro or fluoro;

5  $R^{18}$  is hydrogen or fluoro;

$R^{19}$  is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

$R^{20}$  is hydrogen or fluoro; and

$R^{21}$  is chloro, fluoro, trifluoromethyl or methyl,

10 provided that  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$  and  $R^{20}$  are not all fluoro when  $R^{16}$  is ethyl and  $R^{19}$  is H;

or a prodrug thereof.

30. The method according to claim 29, wherein:

$R^{16}$  is ethyl;

15  $R^{17}$  and  $R^{19}$  are chloro;

$R^{18}$  and  $R^{20}$  are hydrogen, and

$R^{21}$  is methyl;

or a prodrug thereof.

20 31. The method according to claim 1, wherein the amount of duloxetine, venlafaxine or atomoxetine, together with the amount of the cyclooxygenase-2 selective inhibitor or prodrug thereof, constitute an amount effective for the treatment, prevention, or inhibition of the CNS disorder, pain and inflammation, or inflammation-associated disorder.

32. The method according to claim 1, wherein an amount of venlafaxine is within a range from about 37.5 mg/day to about 375 mg/day and an amount of atomoxetine is from about 0.4 mg/kg/day to about 2.0 mg/kg/day based on a body weight of the subject.

5        33. The method according to claim 32, wherein an amount of venlafaxine is within a range from about 75 mg/day to about 225 mg/day and an amount of atomoxetine is from about 0.5 mg/kg/day to about 1.9 mg/kg/day based on a body weight of the subject.

10       34. The method according to claim 33, wherein an amount of venlafaxine is within a range from about 75 mg/day to about 150 mg/day and an amount of atomoxetine is from about 1.2 mg/kg/day to about 1.8 mg/kg/day based on a body weight of the subject.

15       35. The method according to claim 32, wherein the amount of the cyclooxygenase-2 selective inhibitor or prodrug thereof is within a range from about 0.01 to about 100 mg/day per kg of body weight of the subject.

20       36. The method according to claim 35, wherein the amount of the cyclooxygenase-2 selective inhibitor or prodrug thereof is within a range from about 1 to about 20 mg/day per kg of body weight of the subject.

37. The method according to claim 1, wherein the weight ratio of the amount of cyclooxygenase-2 selective inhibitor or prodrug thereof to the amount of duloxetine, venlafaxine or atomoxetine that is administered to the subject is within a range from about 0.1:1 to about 10:1.

25       38. The method according to claim 37, wherein the weight ratio of the amount of cyclooxygenase-2 selective inhibitor or prodrug thereof to the amount of duloxetine, venlafaxine or atomoxetine that is administered to the subject is within a range from about 0.4:1 to about 2:1.

30       39. The method according to claim 1, wherein the pain and inflammation or inflammation-associated disorder is selected from the

- group consisting of neuropathic pain, headache, fever, arthritis, rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus, juvenile arthritis, asthma, bronchitis, menstrual cramps, tendinitis, bursitis, connective tissue injuries or disorders, skin related conditions, psoriasis, eczema, burns, dermatitis, gastrointestinal conditions, inflammatory bowel disease, gastric ulcer, gastric varices, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, cancer, colorectal cancer, herpes simplex infections, HIV, pulmonary edema, kidney stones, minor injuries, wound healing, vaginitis, candidiasis, lumbar spondylanhrosis, lumbar spondylarthrosis, vascular diseases, migraine headaches, sinus headaches, tension headaches, dental pain, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, swelling occurring after injury, myocardial ischemia, ophthalmic diseases, retinitis, retinopathies, conjunctivitis, uveitis, ocular photophobia, acute injury to the eye tissue, pulmonary inflammation, nervous system disorders, cortical dementias, and Alzheimer's disease.
40. The method according to claim 1, wherein the pain and inflammation or inflammation-associated disorder is an ophthalmic disease or ophthalmic injury.
41. The method according to claim 40, wherein the ophthalmic disease or ophthalmic injury is selected from the group consisting of retinitis, retinopathies, conjunctivitis, uveitis, ocular photophobia, and acute injury to the eye tissue.
42. The method according to claim 39, wherein the pain and inflammation or inflammation-associated disorder is arthritis.
43. The method according to claim 42, wherein the arthritis is osteoarthritis.



44. The method according to claim 42, wherein the arthritis is rheumatoid arthritis.

45. The method according to claim 1, wherein the subject is an animal.

5 46. The method according to claim 45, wherein the subject is a human.

47. The method according to claim 2, wherein the cyclooxygenase-2 selective inhibitor or prodrug thereof and duloxetine, venlafaxine or atomoxetine are administered to the subject enterally or  
10 parenterally in one or more dose(s) per day.

48. The method according to claim 47, wherein the cyclooxygenase-2 selective inhibitor or prodrug thereof and duloxetine, venlafaxine or atomoxetine are administered to the subject substantially simultaneously.

15 49. The method according to claim 47, wherein the cyclooxygenase-2 selective inhibitor or prodrug thereof and duloxetine, venlafaxine or atomoxetine are administered sequentially.

50. The method according to claim 1, wherein the CNS disorder is selected from the group consisting of Alzheimer's disease (AD), amnesia,  
20 amyotrophic lateral sclerosis (ALS), anorexia nervosa, anxiety disorder, anxiety neurosis, ataxia, attention deficit hyperactivity disorder, autism, autonomic nervous system disease, behavior disorder, bipolar disorder, brain injury, bulimia, catatonia, central nervous system disease, chronic psychiatric indications, chronic urological indications, incontinence,  
25 cognitive disorder, convulsion, cranial neuropathy, cyclothymia or cyclothymic personality, cystocele, delirium, delusional (paranoid) disorders, dementia, depression, diabetic neuropathy, diverticula, dystonia, dystonia, dysuria, eating disorder, encephalitis, epilepsy, extrapyramidal syndrome, feeding disorder, hematuria, Huntington's  
30 disease (HD) or Huntington's choria, hydronephrosis, hydroureter,

hypochondriacal neurosis, hypomanic personality, hypoxia, hysteria, hysterical neurosis, manic depression, meningitis, mental deficiency, mental disorder, motor neurone disease, movement disorder, muscular spasm, multiple sclerosis, myalgia, name, narcissism, nervous system injury, neurodegenerative disease, neurological disease, neurological, 5 mental and cognitive disorder, neuropathy, obsessive/compulsive disorder, obsessive-compulsive neurosis, opiate use disorder, paralysis, Parkinson's disease (PD), passive-aggressive disorder, personality disorder, phobic neurosis, pneumaturia, posttraumatic stress disorder, psychopathy, psychosis, schizophrenia, seizure, senile dementia, sleep 10 disorder, sociopathy, somatization disorder, stupor, substance dependence, tardive dyskinesia, and tinnitus.

51. A method for the treatment, prevention, or inhibition of a disorder in a subject, comprising administering a cyclooxygenase-2 selective inhibitor or prodrug thereof and duloxetine, venlafaxine or 15 atomoxetine to the subject, wherein the disorder is selected from the group consisting of actinomycosis, acute appendicitis, acute cholecystitis, acute hemorrhagic encephalitis, acute hepatitis, acute injury to the eye tissue, acute myocardial infarction, acute pancreatitis, adenitis, amebiasis, 20 amebic colitis, anal fissures, ankylosing spondylitis, aphthous stomatitis, aphthous ulcers, aplastic anemia, appendiceal abscess, arachnoiditis, arteritis, arthritis, asthma, atherosclerosis, atopic dermatitis, B virus myelitis, "backwash" ileitis of ulcerative colitis, bacterial endocarditis, Behcet's syndrome, berylliosis, blastomyces dermatitidis, blepharitis, brain abscess, 25 bronchiectasis, bronchiolitis, brucellosis, bursitis, cancer and associated pain, candidiasis, carcinoma of the bile ducts, cat-scratch fever, cavernous sinus thrombosis, cecal diverticulitis, cellulitis, cerebral epidural abscess, cholelithiasis, chondritis, choreoretinitis, chronic active hepatitis, chronic urological indications, incontinence, coccidioides immitis, colorectal cancer, 30 conjunctivitis, cortical dementias, cortical thrombophlebitis, Crohn's

disease, cryptococcus neoformans, cystic fibrosis, dacryocystitis, dental pain, dermatomyositis, diabetes mellitus (type 1 and type 2), diabetic neuropathy, diverticula, dysuria, encephalitis, encephalomyelitis, endometritis, endophthalmitis, eosinophilic gastroenteritis, epicondylitis, 5 epiglottitis, erythema multiforme, erythema nodosum, external ear inflammatory disease, fasciitis, fibromyalgia, fistulas, folliculitis, gastric ulcer, gastric varices, gastritis, gingivitis, gliosis, glomerulonephritis, gonococcal infection, gout, granulomatous colitis, hemorrhoids, hepatitis, hematuria, herpes, HIV1, Hodgkin's disease, hypersensitivity, ileal carcinoid, ileitis, 10 ileocecal tuberculosis, ileocolitis, ileojejunitis, iliofemoral venous thrombosis, incarcerated hernia, infarction of the colon, inflammatory bowel disease, interstitial keratitis, intestinal obstruction, iritis, irritable bowel syndrome, ischemia, ischemic colitis, kidney stones, labyrinthitis, lateral sinus thrombosis, leprosy, low back pain, lumbar spondylarthritis, lymphadenitis, 15 lymphangitis, lymphogranuloma inguinale, lymphosarcoma, mastoiditis, mesenteric thrombosis, metastatic melanocarcinoma, migraine headache, minor injuries, multiple sclerosis, myasthenia gravis, myocardial ischemia, myositis, myringitis, nephritis, nephrotic syndrome, neuritis, neuronitis, neuropathic pain, neurosyphilis, nodular lymphoid hyperplasia, ocular 20 photophobia, ocular photophobia, ophthalmic diseases, osteoarthritis, osteomyelitis, otitis, ovarian carcinoma, panencephalitis, papillitis, parenchymatous, pelvic inflammatory disease, perforated ulcer, perianal abscess, periarteritis nodosa, pericarditis, pericholangitis, periodontitis, peritonitis, pharyngitis, pleuritis, pneumaturia, pneumonia, pneumonitis, 25 poliomyelitis, polymyositis, postherpetic neuralgia, prostatitis, pseudomembranous enterocolitis, pseudopolyps, psoriasis, pulmonary edema, pulmonary infarction, pulmonary inflammation, pulpitis, pyelonephritis, pyelephlebitis, pyoderma gangrenosum, rabies, radiation colitis, radiation enteritis, rectal prolapse, regional enteritis, renal 30 amyloidosis, retinitis, retinopathies, rheumatic fever, rheumatoid arthritis,

rhinitis, rickettsiae, sacroiliitis, salpingitis, sarcoidosis, scleritis, sclerodoma, sclerosing cholangitis, septic thrombophlebitis, shigellosis, shingles, sinus headaches, sinusitis, spinal epidural abscess, splenitis, subdural empyema, swelling occurring after injury, syphilitic meningovascular syphilis, tabes dorsalis, tendonitis, tenosynovitis, tension headaches, thyroiditis, tonsillitis, 5 toxic megacolon, transverse myelitis, trigeminal neuralgia, tuberculosis enteritis, typhoid fever, ulcerative colitis, ulcerative proctitis, ureteritis, uveitis, vaginitis, vascular diseases, vascular necrosis, vasculitis, ventricular empyema, vestibulitis, viral infections, wound healing, and Zollinger-Ellison syndrome.

10 52. A method for the treatment or prevention of a disorder having an inflammatory component in a subject in need of said treatment or prevention of disorders having an inflammatory component, the method comprising the step of administering to the subject a therapeutically effective dose of a cyclooxygenase-2 selective inhibitor or a 15 pharmaceutically acceptable salt or prodrug thereof and a compound selected from the group consisting of duloxetine, venlafaxine and atomoxetine.

20 53. A composition for the treatment, prevention, or inhibition of a CNS disorder, pain and inflammation, or an inflammation-associated disorder comprising a cyclooxygenase-2 selective inhibitor or prodrug thereof and a compound selected from the group consisting of duloxetine, venlafaxine and atomoxetine.

25 54. The composition according to claim 53, wherein the composition is useful for treating a subject in need of treatment, prevention, or inhibition, of a CNS disorder, pain and inflammation, or an inflammation-associated disorder, and wherein a dose of the composition constitutes an amount of a cyclooxygenase-2 selective inhibitor or a 30 pharmaceutically acceptable salt or prodrug thereof and an amount of a compound selected from the group consisting of duloxetine, venlafaxine

and atomoxetine, wherein the amounts together constitute a CNS disorder, pain and inflammation, or inflammation-associated disorder suppressing treatment, prevention, or inhibition effective amount.

5        55. The composition according to claim 53, wherein the cyclooxygenase-2 selective inhibitor or prodrug thereof and duloxetine, venlafaxine or atomoxetine are present in a combination of the cyclooxygenase-2 selective inhibitor and duloxetine, venlafaxine or atomoxetine as described in any one of claims 3 - 29 and 24 - 38.

10       56. A pharmaceutical composition comprising a cyclooxygenase-2 specific inhibitor or prodrug thereof; a compound selected from the group consisting of duloxetine, venlafaxine and atomoxetine; and a pharmaceutically-acceptable excipient.

15       57. The pharmaceutical composition according to claim 56, wherein the cyclooxygenase-2 selective inhibitor or prodrug thereof and duloxetine, venlafaxine or atomoxetine are present in a combination of the cyclooxygenase-2 selective inhibitor or prodrug thereof and duloxetine, venlafaxine or atomoxetine as described in any one of claims 3 - 29 and 24 - 38.

20       58. A kit that is suitable for use in the treatment, prevention or inhibition of a CNS disorder, pain and inflammation, or an inflammation-associated disorder, wherein the kit comprises a first dosage form comprising a cyclooxygenase-2 selective inhibitor or prodrug thereof and a second dosage form comprising a compound selected from the group consisting of duloxetine, venlafaxine and atomoxetine, in quantities that  
25       comprise a therapeutically effective amount for the treatment, prevention, or inhibition of a CNS disorder, pain and inflammation, or inflammation-associated disorder.

59. The method according to claim 1, wherein an amount of duloxetine is within a range from about 37.5 mg/day to about 375 mg/day

and an amount of atomoxetine is from about 0.4 mg/kg/day to about 2.0 mg/kg/day based on a body weight of the subject.

5        60.    The method according to claim 59, wherein an amount of duloxetine is within a range from about 75 mg/day to about 225 mg/day and an amount of atomoxetine is from about 0.5 mg/kg/day to about 1.9 mg/kg/day based on a body weight of the subject.

10       61.    The method according to claim 60, wherein an amount of duloxetine is within a range from about 75 mg/day to about 150 mg/day and an amount of atomoxetine is from about 1.2 mg/kg/day to about 1.8 mg/kg/day based on a body weight of the subject.

      62.    The method according to claim 59, wherein the amount of the cyclooxygenase-2 selective inhibitor or prodrug thereof is within a range from about 0.01 to about 100 mg/day per kg of body weight of the subject.

15       63.    The method according to claim 62, wherein the amount of the cyclooxygenase-2 selective inhibitor or prodrug thereof is within a range from about 1 to about 20 mg/day per kg of body weight of the subject.

20       64.    The method according to claim 1, wherein an amount of duloxetine is within a range from about 37.5 mg/day to about 375 mg/day and an amount of venlafaxine is from about 0.1 mg/kg/day to about 5 mg/kg/day based on a body weight of the subject.

25       65.    The method according to claim 64, wherein an amount of duloxetine is within a range from about 75 mg/day to about 225 mg/day and an amount of venlafaxine is from about 0.2 mg/kg/day to about 4 mg/kg/day based on a body weight of the subject.

30       66.    The method according to claim 65, wherein an amount of duloxetine is within a range from about 75 mg/day to about 150 mg/day and an amount of venlafaxine is from about 0.5 mg/kg/day to about 2 mg/kg/day based on a body weight of the subject.

67. The method according to claim 64, wherein the amount of the cyclooxygenase-2 selective inhibitor or prodrug thereof is within a range from about 0.01 to about 100 mg/day per kg of body weight of the subject.

- 5           68. The method according to claim 67, wherein the amount of the cyclooxygenase-2 selective inhibitor or prodrug thereof is within a range from about 1 to about 20 mg/day per kg of body weight of the subject.